IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

THE PROCTOR & GAMBLE COMPANY	:	
	:	
Plaintiff,	:	
	:	
v.	:	Civil Action No. 04-940-JJF
	:	
TEVA PHARMACEUTICALS USA, INC.	:	
	:	
Defendant.	:	

William F. Lee, Esquire, David B. Bassett, Esquire, and Vinita Ferrera, Esquire of WILMER CUTLER PICKERING HALE AND DORR, Boston, Massachusetts.
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OPINION

February 28, 2008
Wilmington, Delaware

Farnan, District Judge.

INTRODUCTION

This action was filed by The Proctor & Gamble Company ("Proctor & Gamble") against Teva Pharmaceuticals USA, Inc. ("Teva"), alleging patent infringement. Proctor & Gamble's original Complaint, filed on August 13, 2004, alleged that Teva's efforts to market a generic version of risedronate sodium infringed on United States Patent Nos. 5,538,122 ("the '122 Patent") and 6,096,342.[1] (D.I. 1.) On August 25, 2004, Proctor & Gamble amended its Complaint to limit its infringement allegations to only the '122 Patent. (D.I. 5.)

Proctor & Gamble is the owner by assignment of the '122 Patent, entitled "Pharmaceutical Compositions Containing Geminal Diphosphonates." (JTX 1.) The '122 Patent issued on December 10, 1996, eleven years after Proctor & Gamble filed a supporting application with the U.S. Patent and Trademark Office ("PTO"). The '122 Patent expires on December 10, 2013. (D.I. 1.) The claims at issue describe the compound 2-(3-pyridyl)-1-hydroxyethane diphosphonic acid ("risedronate"). (JTX 1.)

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[1] On the same day that Proctor & Gamble instituted the present action, Merck & Co. brought a separate action in this District alleging patent infringement stemming from the same ANDA filing. See Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc., Civil Action No. 04-939-GMS. Teva requested consolidation of the present action and the Merck action. (D.I. 11.) This Court declined to consolidate. (D.I. 22; D.I. 321.)

Proctor & Gamble has listed the '122 Patent in the Federal Food and Drug Administration's ("FDA") publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") in connection with 5 mg, 30 mg and 35 mg dosages of risedronate sodium, which Proctor & Gamble commercially markets as Actonel®. (D.I. 1.) Actonel® is marketed for the treatment and prevention of osteoporosis, and for the treatment of Paget's Disease.

By letter dated July 2, 2004, Teva notified Proctor & Gamble that it had submitted an Abbreviated New Drug Application ("ANDA"), No. 77-132, to the FDA seeking approval to manufacture, use, and market generic risedronate sodium tablets in the same doses as Actonel® before the expiration of the '122 Patent. Included with Teva's ANDA filing was a "paragraph IV certification" (21 U.S.C. § 355(j)(2)(A)(vii)(IV)) asserting that, in Teva's opinion, the '122 Patent is invalid, unenforceable, or would not be infringed by the commercial marketing of the proposed risedronate sodium tablets. After receiving Teva's ANDA notice letter, Proctor & Gamble brought this timely action within the forty-five day statutory period, alleging patent infringement and seeking a declaration that the '122 Patent is valid and enforceable.

By stipulation signed by the Court on November 6, 2006, Proctor & Gamble declared that it would only pursue judgment with

respect to claims 4, 16 and 23 of the '122 Patent. (D.I. 86.) By stipulations signed by the Court on January 27, 2006 and November 6, 2006, Teva stipulated that, for purposes of this action, the manufacture and marketing of generic risedronate sodium tablets would infringe those claims. (D.I. 63, 86.) The only remaining issue in this action is the validity of claims 4, 16, and 23 of the '122 Patent.

The Court has jurisdiction over the parties and the subject matter pursuant to 28 U.S.C. § 1338(a). Additionally, venue is appropriate under 28 U.S.C. §§ 1391 and 1400(b). Neither jurisdiction nor venue are contested by the parties. The Court conducted a bench trial from November 6, 2006 to November 9, 2006. This Memorandum Opinion constitutes the Court's findings of fact and conclusions of law on the issues raised during trial.

II. The Parties Contentions

Teva challenges the validity of the '122 patent on the basis of obviousness under 35 U.S.C. § 103. In particular, Teva contends that the '122 patent is obvious in light of U.S. Patent 4,761,406, entitled "Regiment for Treating Osteoporosis" (the "'406 Patent"). In the alternative, Teva contends that the '122 Patent is invalid for obviousness-type double patenting. Specifically, Teva contends that the structural similarities between risedronate and 2-pyr EHDP render the relevant claims of the '122 patent patentably indistinct from claim 15 of the '406

patent.

In response, Proctor & Gamble contends that the '122 patent is not invalid, because at the time risedronate was invented, the idea of synthesizing that compound was not obvious to a person of ordinary skill in the art. Proctor & Gamble also contends that the '406 patent is not properly considered prior art for purposes of Teva's invalidity arguments, and in any event, the '406 patent claims subject matter different than that claimed in the '122 patent.

SUMMARY OF THE EVIDENCE ADDUCED AT TRIAL

I. Teva Witnesses

A. Dr. George R. Lenz

1. Background

Doctor George R. Lenz has over forty years of experience in medicinal chemistry. He received a Bachelor of Science degree in Chemistry from the Illinois Institute of Technology in 1963. Dr. Lenz attended the University of Chicago, receiving a Master of Science in Physical Science, with a chemistry emphasis, in 1965, and a Ph.D. in Organic Chemistry in 1967. These degrees were followed by fellowships at the Yale University National Cancer Institute and the University of Geneva (Switzerland). Currently Dr. Lenz heads GRLEN R&D Associates, a company which provides consulting services in medicinal chemistry as well as drug discovery and development assistance to small companies

interested in small molecules. His appearance at this trial was his first appearance as a retained expert witness.

2. Opinion

Dr. Lenz opined that the '406 Patent describes general bisphosphonates, and in so doing, reveals 2-pyr EHDP as the most potent of the compounds listed therein. (Lenz 88, 90.) With respect to the '122 patent, Dr. Lenz understood the subject matter to be the use of bisphosphonate compositions in treating abnormal calcium and phosphate metabolism. (Lenz 68.)

To Dr. Lenz, a person of ordinary skill in the art for purposes of an obviousness inquiry would have a Ph.D. in chemistry, several years of experience in the pharmaceutical industry, experience with drug discovery and design, and particularized experience interpreting activity and toxicity results of new compounds. (Lenz 77-79.) He did not believe that a person of ordinary skill in the art would need to be an organophosphorous chemistry specialist. (Id.) Rather, he testified, that the person should be a medicinal chemist with bisphosphonate knowledge and experience.

Even by his own definition, Dr. Lenz admitted he was not a person of ordinary skill in the art in the mid-1980s. (Lenz 203.) Until preparing for the present case, Dr. Lenz had no specialized experience in the area of bisphosphonates. (Lenz 154, 203.) He has never synthesized bisphosphonates, and until Teva retained

him for this case, he was unfamiliar with the structural mechanics of bisphosphonates, and the tests used to interpret their activity and toxicity. (Lenz 154-166, 176.)

However, Dr. Lenz believed that in preparing for this trial he had acquired enough contemporary knowledge to retrospectively understand what a medicinal chemist would have known about bisphosphonates in the mid-1980s. (Lenz 203.) Dr. Lenz thought he was qualified to make this assessment after comparing the disputed patent claims, reviewing the available literature regarding what knowledge medicinal chemists familiar with bisphosphonates would have had in the mid-1980s, reviewing patents for other drugs with pyridyl rings, and applying his own medicinal chemistry experience. (Lenz 95.)

With the above knowledge and qualifications, Dr. Lenz opined that risedronate would have been obvious to medicinal chemists in the mid-1980s. He testified that the job of a medicinal chemist is to dissect molecules, identify their molecular components, and rearrange or substitute each molecular component, with the goal of creating new compounds with optimal properties. (Lenz 71.) Dr. Lenz opined that medicinal chemists, when working with bisphosphonates as a class, would try to make structural alterations to the tails of compounds while preserving the bone lividity inherent in the head. (Lenz 72:16-20.) The result of this routine practice, when applied to a hydroxyethane

bisphosphonate, would be that a medicinal chemist would, "upon seeing one active compound with a [pyridyl ring], would automatically make the other two positional isomers, having a strong expectation of success in having similar activities." (Lenz 105:8-12.) According to Dr. Lenz, synthesis of the additional isomers would only require minor alterations, and would be obvious given the expectation that the isomers would have at least some activity. (Lenz 97.) To support this conclusion, Dr. Lenz referred to eight other patents covering drugs marketed in 1985 that had pyridyl rings. Each drug was patented, and each patent claimed the active drug and at least one other positional isomer. (Lenz 98-105.) Thus, in light of the propensities of medicinal chemists, the presence of a pyridyl ring in compounds at issue, and the pattern of other inventors claiming multiple positional isomers in other patents available at the time, Dr. Lenz concluded that a medicinal chemist aware of 2-pyr EHDP from the '406 patent would have found risedronate to be an obvious modification with a reasonable expectation of success and few surprising differences from its other isomers. (Lenz 95-97, 120.)

Dr. Lenz's expert opinion regarding the obviousness of the '122 Patent hinges on his view of a person of ordinary skill in the art; if a different definition is adopted, his basis for obviousness fails. (Lenz 199.) The Court notes that Dr. Lenz's

view is very narrow, and excludes some of the leaders in bone disease and bisphosphonate research in the mid-1980s. For example, Dr. Herbert Fleisch, an esteemed bisphosphonate pioneer, was not a medicinal chemist and therefore would not qualify as a person of ordinary skill in the art according to Dr. Lenz's testimony. When asked about some of Dr. Fleisch's opinions about bisphosphonates, such as his position that it was "dangerous and misleading" to "infer from one compound the effects in another," Dr. Lenz testified that Dr. Fleisch was only partially correct. (Lenz 233, 237.) In Dr. Lenz's view, a medicinal chemist would have understood that Dr. Fleisch was referring to the unpredictability between classes of compounds, not between individual compounds. (Lenz 240-43.) However, Dr. Lenz was unable to point to any other scholar who viewed Dr. Fleisch's comment the same way.

B. Dr. Jesse David

1. Background

Dr. Jesse David specializes in economic analysis related to commercial disputes, with a particular focus on intellectual property litigation. He received a Bachelor of Science in Economics from Brandeis University in 1991 and a Ph.D. in Economics from Stanford University in 2000. Dr. David is currently the Vice President of National Economic Research Associates ("NERA"), where he has worked since 1997.

2. Opinion

Dr. David was called to testify as Teva's expert on the commercial success of risedronate. In so doing, he did not contest that risedronate is a commercial success. (David 301:10-21.) Rather, he testified that when there is "imperfect knowledge" in a marketplace, the commercial success of a patented product has limited bearing on whether the product was obvious or not. (David 295, 298-99.) Thus, in Dr. David's opinion, because Proctor & Gamble was the only entity with knowledge of the relevant prior art, and therefore the only entity with the ability to make the jump from 2-pyr EHDP to risedronate, commercial success is not a relevant factor in determining the '122 Patent's validity. (David 298-99.)

Dr. David's testimony was based on two assumptions: 1) that the '406 Patent and the 2-pyr EHDP compound are the prior art relevant to the '122 Patent, and 2) that at the time risedronate was made, Proctor & Gamble was the only entity with knowledge of this prior art. (David 297-98, 328.) Dr. David never conducted personal evaluations of whether these assumptions were justified, and could not offer any opinions on the relevance of commercial success to the validity inquiry if either of his assumptions were untrue. (David 325, 327.)

Dr. David testified that a commercial success analysis is not relevant to the instant validity inquiry. (David 298.) Based

on his assumptions, 2-pyr EHDP was a trade secret known only to Proctor & Gamble at the time risedronate was invented, and Proctor & Gamble was the only inventor capable of making the jump from the '406 Patent to the '122 Patent because "the other parties that could have made the invention simply didn't have the basis, the starting point from which to perhaps pursue an incentive to invent the '122 Patent and the compounds contained in it." (David 298-99.) For commercial success to have any analytical relevance, Dr. David testified that other inventors in the marketplace would have needed the chance to make risedronate as well. (David 297.) Because they did not, it is Dr. David's opinion that Actonel®'s commercial success cannot speak to the obviousness or non-obviousness of synthesizing risedronate.

On cross examination, Dr. David testified that he had spent less than twenty hours, cumulatively, working on the two expert reports he prepared for Teva. (David 310-311.) He attributed the limited hours, in part, to the "significant" background he had already developed from working for Teva in Merck Pharmaceutical's case dealing with the same ANDA filing,[2] but he did not explain why he did not review any information on Actonel®, the drug at issue in this case. (David 310-312.) Moreover, Dr. David admitted that his preparation did not involve any independent analysis into whether Actonel® was a commercial success, whether

[2] See note 1.

2-pyr EHDP was prior art, whether Proctor & Gamble actually was the only entity with knowledge of 2-pyr EHDP at the time risedronate was invented, or whether the discovery of 2-pyr EHDP was a necessary prerequisite to the discovery of risedronate. (David 301, 317, 326, 328, 330.)

Dr. David also testified that his amended expert report made critical assumptions that, if incorrect, would negate his report and opinion. In essence, Dr. David testified that he would not have any opinion on the importance of commercial success if any of his assumptions was not correct. (David 325.)

II. Proctor & Gamble Witnesses

A. Dr. John P. Bilezikian

1. Background

Dr. John Bilezikian received his Bachelor of Arts degree from Harvard College in 1965, graduating *magna cum laude* with an emphasis in Biochemistry. (PTX 428.) Thereafter, Dr. Bilezikian received an M.D. from the College of Physicians & Surgeons, Columbia University in 1969. (Id.) Dr. Bilezikian is currently a professor of Medicine and Pharmacology at the College of Physicians and Surgeons, Columbia University, as well as the director of Columbia's endocrinology program. (Id.) His research career has primarily focused on metabolic bone diseases. (Bilezikian 347.) Dr. Bilezikian belongs to, and has taken leadership roles in, a number of metabolic bone disease societies

and journals. (PTX 428.)

2. Opinion

Dr. Bilezikian was called to offer opinions on the state of metabolic bone disease research in the mid-1980s as well as on Actonel®'s present clinical success. After providing an overview of the process of bone remodeling and the negative effects of osteoporosis, he testified that osteoporosis treatments were stagnant until the early 1980s. At that time, the bisphosphonate class emerged as a possible treatment for osteoporosis. (Bilezikian 349-66.) The first two promising bisphosphonates, etidronate and clodronate, had clinical problems preventing their commercialization. (Bilezikian 378-79.) Yet, their discovery motivated drug companies, including Proctor & Gamble, to search for new bisphosphonates that could better treat osteoporosis. The search "was an empirical trial and error science. You could not infer function from structure." (Bilezikian 390-91.) Thus, Dr. Bilezikian testified, there was "no way scientists working in the area of metabolic bone disease would have been able to predict the clinical effects or other properties attributed to different bisphosphonates." (Bilezikian 390.)

On cross examination, Dr. Bilezikian agreed that scientists in the mid-1980s understood that bisphosphonates, as a general class, were active in inhibiting bone resorption. (Bilezikian 410.) They could also have reasonably expected different members

of the class, including 2-pyr EHDP and risedronate, to have at least some activity in affecting bone resorption. (Id.) Further, scientists in 1985 knew that the addition of a hydroxy group to the bisphosphonate part of a molecule would likely improve the compound's function. (Bilezikian 408.)

Dr. Bilezikian next opined about the present clinical success of Actonel®. His opinions were based upon anecdotal encounters with patients and personal belief, so he could not support them with any proof. Nonetheless, he suggested that physicians often choose to prescribe Actonel® because they, like he, believe it is effective in reducing major bone fractures while also being sensitive to patients' gastro-intestinal tracts. (Bilezikian 387.) Moreover, though there has not been a head-to-head study comparing risedronate with the two other bisphosphonates approved to treat osteoporosis in the United States, alendronate and ibandronate, Dr. Bilezikian's opinion was that Actonel® is the most sensitive to the gastro-intestinal tract, the least likely to cause frozen bone, and the least involved in osteoporosis of the jaw. (Bilezikian 388-390, 399-400.) Dr. Bilezikian also opined that patients perceive Actonel® the same way, which further contributes to Actonel®'s success. (Bilezikian 387.)

B. Dr. James J. Benedict

1. Background

Dr. James Benedict has worked with bisphosphonates since 1971, and has focused on using bisphosphonates to treat bone diseases since 1974. He has a bachelors degree and Ph.D. in Chemistry from the University of Wisconsin, Madison. Dr. Benedict worked at Proctor & Gamble between 1971 and 1986. He is the inventor of 2-pyr EHDP and risedronate, and is listed as an inventor of the '122 Patent.

2. Opinion

Dr. Benedict was called to testify about his role in inventing 2-pyr EHDP and risedronate. His search for a bisphosphonate that would effectively treat metabolic bone diseases started in 1974. He began working with the first two bisphosphonates found to improve metabolic bone diseases, etidronate and clodrinate, and structurally altered the head portions of these molecules. (Benedict 424-25.) Over time, he created new bisphosphonate families by making changes to other parts of the molecules, including the tail. (Id.) This gradual trial and error approach of familial creation was typical at Proctor & Gamble.

Scientists would "typically . . . make a member of a family and send it out for investigation and if it looked reasonable, [they] would make more in that same family." (Benedict 427.)

Ultimately, through this approach, Proctor & Gamble researchers synthesized hundreds of new bisphosphonate compounds because they could not predict the efficacy or toxicity levels of the new compounds, and "kept getting surprised and tried to refine [their] hypothesis about what was going to be good." (Benedict 428.)

Dr. Benedict also testified about his recollection of the conception and reduction to practice of 2-pyr EHDP and risedronate. In May 1984, he had the idea of converting ethane diphosphonate (EDP) to hydroxyethane diphosphonate (EHDP) "just to see what increasing the affinity for bone would do." (Benedict 451.) Nearly a year later, in March 1985, the idea was tested and 2-pyr EHDP was synthesized. (Benedict 452.) Because Proctor & Gamble scientists had no idea what the compound's toxicity or potency would be, they sent it out for testing. (Id.) The test results were returned in March 1985 and indicated toxicity problems, so his team set out to "modulate that toxicity by changing the structure of other family members." (Benedict 461.) Company notebooks and idea books belonging to Dr. Benedict show that a wide variety of compounds were conceived and tested, and many were rejected. However, one of the compounds conceived of during this search was risedronate. Risedronate appears in one of Dr. Benedict's notebooks, on a page dated "5/3/85." (PTX 67.) This page is unsigned and unwitnessed because of what Dr.

Benedict recognized as a bad habit of viewing Proctor & Gamble's notebook authenticating process as a hassle. (Benedict 505, 507.) Though he did not always sign every lab page, Dr. Benedict's typical habit when work carried over several pages was to sign the last page of the work.[3] (Benedict 508:19-24.) That was the case on May 3, 1985 as well. (Id.) After being conceived of on May 3, 1985, and subsequently synthesized, risedronate was sent out for testing in early June so the team could assess the compound's properties. (Benedict 468-69.) Though Dr. Benedict testified at trial that he was surprised by the test results, (Benedict 520-21), he testified in an earlier deposition that he had not been surprised given his knowledge of the relationship between alendronate and pamidronate, two isomers that were both effective in treating bone disease. (Benedict 521, quoting Benedict Depo. 152.)

Dr. Benedict was not involved in the development of the '406 patent. Its inventors, Larry Flora and Benjamin Floyd, worked in a different department at Proctor & Gamble. (Benedict 461-62.) Flora and Floyd listed the recently synthesized 2-pyr EHDP as one of the compounds that could potentially be used with the claimed dosing regimen, but they also included the testing data indicating 2-pyr EHDP's toxicity problems. (JTX 5.) While

[3] While the last page of this entry was signed, but not witnessed, the lab pages in question also had notes on them which were made at later dates. These notes were not dated or signed.

acknowledging the possibility that he talked with Flora and Floyd about the use of bisphosphonates in treating bone disease, Dr. Benedict could not specifically recall any conversations to that effect. (Benedict 222-23.)

When asked on cross-examination about unsynthesized compounds listed in the '122 Patent, Dr. Benedict's trial testimony did not entirely compliment his deposition testimony. At trial, Dr. Benedict testified that he did not believe the '122 Patent included compounds that had not been synthesized at the time of the patent application. (Benedict 493.) However, in his deposition testimony, Dr. Benedict conceded the possibility that not all of the compounds disclosed in the '122 Patent had been synthesized at the time of the patent application (Benedict 496, citing Benedict Depo. pg. 177, line 20.) Dr. Benedict also testified at deposition that unsynthesized compounds could have been listed "[b]ecause we would have thought it would have expectations, it would have had similar biology." (Benedict 497-98, Depo 178, line 15-22.) Further, the position he took in his deposition was that one sign of similar biology would have been "[t]hat it was structurally similar. It might have been a two rather than a three substitution on a ring or something such as that." (Id.)

C. Dr. Charles E. McKenna

1. Background

Dr. Charles McKenna has professionally focused on organophosphorous chemistry since the early 1970s. He is currently a Professor of Chemistry and Pharmaceutical Sciences at the University of Southern California. He received a Bachelor of Art degree from Oakland University in 1966, co-majoring in French Literature and Chemistry. He received a Ph.D. in Chemistry from the University of California, San Diego in 1971. Dr. McKenna founded and now serves as director of the Interdisciplinary Program in Drug Discovery ("IPIDD") at the University of Southern California. He also serves on the International Scientific Board for the International Conference in Phosphorous Chemistry.

2. Opinion

Dr. McKenna was called to offer his expert opinion on the qualifications and knowledge of a person of ordinary skill in the art in the mid-1980s as anticipated by the '122 Patent. Unlike Dr. Lenz, Dr. McKenna did not believe training in medicinal chemistry was necessary. (McKenna 558, 637.) Rather, he proposed that a person of ordinary skill in the art in 1985 needed a Ph.D. in synthetic or bio-organic chemistry and training in the field of organophosphorous chemistry, either through post-doctoral training or industrial experience. (McKenna 555, 558.) Dr. McKenna testified that, by his definition, he was a person of

ordinary skill in the art in the mid-1980s. (McKenna 558.)

Dr. McKenna next testified about the recent advances scientists have made in understanding bisphosphonates. Researchers have only begun to clearly understand the effects of structurally modifying bisphosphonate molecules within the past five years. (McKenna 563-65.) Dr. McKenna testified that without this new understanding to guide their efforts, it would have been impossible for those of ordinary skill in the art in 1985 to predict a bisphosphonate compound's utility, efficacy, or toxicity simply by looking at its structure. (Id.) However, he admitted on cross examination that a chemist researcher aware of 2-pyr EHDP would have known enough about bisphosphonates to expect the next positional isomer, risedronate, to have at least some bone resorption activity. (McKenna 689, 692.)

Though conceding a theoretical possibility of activity, Dr. McKenna opined that such a possibility should not be used as the basis for an obviousness inquiry. Focusing instead on whether researchers could have expected to make a good drug, Dr. McKenna testified that risedronate was not an obvious modification of the '406 Patent under this inquiry because researchers had no basis to expect it to be as good as or better than 2-pyr EHDP. (See McKenna 596.) The '406 Patent simply listed several structurally diverse compounds and did not contain anything that would have singled out 2-pyr EHDP as a compound to be used for treating

osteoporosis. (McKenna 614.) Thus, according to Dr. McKenna, a person of ordinary skill in the art could not have looked at the '406 Patent and developed a reasonable expectation that modifying 2-pyr EHDP would have produced an improved, safe, and effective osteoporosis drug. (McKenna 615-16, 633.)

Dr. McKenna was asked for his opinions about Dr. Fleisch's opinions and writings regarding the uniqueness of individual bisphosphonate compounds. Dr. McKenna opined that Dr. Fleisch was certainly a person of more than ordinary skill in the art in the mid-1980s, and that he was absolutely correct, by 1985 standards, when he wrote that every bisphosphonate compound is unique and its attributes cannot be predicted by looking at the structure of other compounds. In Dr. McKenna's opinion, Dr. Fleisch was talking about individual compounds, not classes of compounds. (McKenna 572-73.) Dr. McKenna also testified that he did not believe that counting the number of carbons in a chain could have helped a chemist in 1985 to predict the efficacy of a bisphosphonate compound. (McKenna 621.)

Finally, Dr. McKenna discussed the eight patents for non-bisphosphonate pyridyl ring compounds that were introduced by Dr. Lenz. Dr. McKenna explained that he looked through patent literature from 1975 to 1985 for compounds with 2, 3, or 4 pyridyl compounds for see if Dr. Lenz was presenting a representative sample of patents. (McKenna 628.) From this

review, he found a total of fifteen patents meeting those criteria. Only three discussed and included research data on all three possible isomers. However, other patents did reference all isomers. (McKenna 677.) Referencing a compound or isomer, while different from synthesizing and testing a compound, does at least indicate that the inventor conceived of the structure. (McKenna 680.) Dr. McKenna did not directly respond to most questions posed to him about whether it would be common for a chemist who develops a pyridine compound to conceive of and make all three isomers. See (McKenna 678-680.)

D. Jocelyn McOsker

1. Background

Ms. McOsker holds a Bachelor of Art degree from Hope College and a Masters degree in Biochemistry from Cornell University. She began working with the Proctor & Gamble New Bone Group in May, 1985, and was responsible for administering bisphosphonate efficacy tests for several bisphosphonate compounds, including risedronate.

2. Testimony

Ms. McOsker testified about her role in Proctor & Gamble's development of new bisphosphonates, namely risedronate. Because she was part of the team that administered TPTX and Shenck assays for newly synthesized bisphosphonates, Ms. McOsker was asked to interpret efficacy test records for 2-pyr EHDP and risedronate,

despite never actually conducting tests for 2-pyr EHDP. See (McOsker 715, 745, 747.) As for 2-pyr EHDP, Ms. McOsker testified that the notebooks reveal that TPTX testing began in September 1985, and Shenck assay testing began in August 1986. (McOsker 725.) According to Ms. McOsker, the fact that lab results showed 2-pyr EHDP to be toxic at a 1 mg P/kg/day dose was disappointing, since for both etidronate and clodrinate 1 mg/P/kg/day was an effective dose. (McOsker 473.)

With respect to risedronate, Mr. McOsker testified about her role in administering the tests, and her surprise when the results indicated that risedronate was a very potent but not overly toxic drug. (McOsker 726-27.) Though she offered testimony about the results of the TPTX tests and Shenck assays conducted for 2-pyr EHDP and risedronate, Ms. McOsker also acknowledged that Shenck or TPTX results from multiple compounds could not be compared to reveal which compound would work best for treating osteoporosis in humans. (McOsker 759-760.)

E. Dr. David Eastman

1. Background

Dr. David Eastman, a toxicologist, received a Bachelor of Science degree in Animal Science and a Ph.D. in Pharmacology and Toxicology from the University of California, Davis. He left Proctor & Gamble after twenty-four years to become the Senior Director of Safety Sciences at Charles River Laboratories in

2006. For most of his time at Proctor & Gamble, Dr. Eastman's toxicology work was focused on bisphosphonates, where he designed Proctor & Gamble's short-term toxicity testing program.

2. Testimony

Dr. Eastman created a short term toxicity screen for Proctor & Gamble that only required a limited amount of resources yet returned quick and reliable data on a large number of compounds. (Eastman Tr. 770-71, 796-98.) The screen was designed to provide useful information with only 2 mg. of each compound and four rats per test group. Though using more rats per group would have been ideal, reliable results could still be obtained through his system, even if one or two rats (of the four) were lost during testing. (Eastman Tr. 798.) Dr. Eastman testified that the short-term screen "provides information that you can use to look at compounds relative to each other to elucidate their primary toxicities," whereas longer term toxicity screens exist primarily to support safety testing. (Eastman Tr. 771-72.) He also testified that acute toxicity tests, such as this short-term screen, are the typical first step in the development of pharmaceutical drugs. (Eastman Tr. 826.)

According to Dr. Eastman, both 2-pyr EHDP and risedronate went through this short-term toxicity screen, and the compounds returned significantly different results. (Eastman Tr. 782-84.) The highest dose at which 2-pyr EHDP did not exhibit toxic

effects was 0.25 mg P/kg/day, whereas 0.75 mg P/kg/day of risedronate could be administered to the test group before toxic effects were observed. To Dr. Eastman, these results suggested that 2-pyr EHDP had a lesser chance of clinical success than risedronate. (Eastman Tr. 795-96.) To other Proctor & Gamble scientists, however, the short-term toxicity screen was not nearly as revealing. To those scientists, the short-term toxicity screen is only useful in predicting unacceptably toxic drugs, not clinically successful drugs. (Eastman Tr. 809, 811.)

F. Dr. Scott C. Miller

1. Background

Dr. Scott Miller received a Bachelor of Science in Biology in 1970 and a Ph.D. in Anatomy in 1974 from the University of Utah. (Miller 831-32, PTX 432.) Currently, he is a Research Professor of Radiobiology and the Director of the Radiobiology Division at the University of Utah. (Miller 831.) He is also a Research Professor of Civil and Environmental engineering and an Adjunct Professor of Exercise and Sports Science and Nutrition at the University of Utah. (Id.) Dr. Miller has been working with bisphosphonates since the early 1970s, and specializes in radiobiology, bone diseases, and preclinical studies of bone physiology, bone metabolism, bone endocrinology and pharmacology. (Miller 832, 837.)

2. Opinion

Dr. Miller, who did not contest that he would not qualify as a person of ordinary skill in the art under either definition offered by the parties, was also called by Proctor & Gamble to discuss the lack of knowledge about bisphosphonate structure/activity relationships in the 1980s. (Miller 929.) He, like those before him, testified that very little was known in 1985 about how a bisphosphonate's structure related to its activity. (Miller 838.) Thus, according to Dr. Miller, it was impossible in the 1980s to look at a bisphosphonate's structure and then predict its safety and efficacy. (Id.)

Dr. Miller also testified that toxicity screening can be used to rank drugs based upon their relative toxicity ranges. See Miller 928.) After explaining the Shenck and TPTX assays, he concluded that the lowest effective doses ("LED") of 2-pyr EHDP and risedronate could be ranked against each other even though they were derived from different assays, and despite the fact that the compounds were tested at different doses. (Miller 858-59, 864.) Finally, Dr. Miller testified that the footnote in Table III of the '406 Patent suggests 2-pyr EHDP is a very toxic compound. (Miller 874, JTX 5.) Thus, in his opinion, the '406 Patent does not suggest that modifying 2-pyr EHDP will produce a more effective therapeutic compound.

G. Dr. Daniel C. Smith

1. Background

Dr. Daniel Smith received a Bachelor of Science in Business Administration in 1980 and a Master of Business Administration in 1982 from the University of Toledo. He received his Ph.D. in Business Administration, with a focus on Marketing and strategy, from the University of Pittsburgh in 1988. (PTX 434.) Dr. Smith is currently Dean of the Kelly School of Business and a Professor of Marketing at the University of Indiana. Since arriving at the University of Indiana, Dr. Smith has taken a leadership role in developing "Healthcare Academy," a two-day workshop for MBA candidates that broadly covers all aspects of the health care industry. Dr. Smith has previously been retained as a consultant and an expert witness for Eli Lilly.

2. Opinion

Dr. Smith was called to discuss the significance of Actonel®'s commercial success. He opined that Actonel® is a commercial success in the United States market, and that its success is due to its patented features. (Smith 1016.)

Dr. Smith testified that physicians base their prescribing decisions on "hard evidence," and "[are not] susceptible to persuasive influence" from pharmaceutical marketing. (Smith 955, 58.) Thus, in his opinion, marketing aimed at physicians is more informative than the "persuasive [ads] that we often see in day

to day TV ads." (Smith 959.) Thus, Dr. Smith opined that Proctor & Gamble's Actonel® marketing efforts, to which more than $1 billion has been dedicated, were intended not to persuade the general lay population but to inform physicians. Accordingly, Dr. Smith concluded that Actonel® has amassed $2.7 billion in aggregate domestic sales because doctors began prescribing it after being informed of its patented features and positive effects on patients. (Smith 1013.)

On cross examination, Dr. Smith admitted that he may have seen a few consumer-oriented magazine ads, but that his preparation and analysis was focused on print advertisements directed toward physicians. He also testified that he ignored typical mediums for persuasive advertising, such as TV, radio, and the internet. (Smith 997, 958.) Moreover, Dr. Smith's commercial success opinions were based exclusively on the United States market. (Smith 1012.) Dr. Smith testified that Actonel® is a commercial success in the United States as gauged by both internal and external factors. Internally, Actonel® exceeded Proctor & Gamble sales estimates by 40-50%. (Smith 966-67.) Externally, Actonel® has had strong sales levels, impressive market share growth, and a large number of refills issued. (Smith 962.) This has led to Actonel®'s impressive aggregate domestic sales and a significant market-share foothold despite entering the market several years after the biggest competitors, Fosamax

and Evista. (Smith 965.)

In forming his expert opinion, Dr. Smith assumed Actonel® was formally launched in 2000, and did not know whether Proctor & Gamble had begun marketing it any earlier. All of the data he looked at suggested a mid-2000 launch, and he did not look for or analyze any information predating that assumed launch date. Finally, Dr. Smith did not opine on the importance of risedronate's commercial success to the present validity inquiry.

DISCUSSION

I. Whether the '122 Patent is Invalid as Obvious under 35 U.S.C. § 103

In pertinent part, 35 U.S.C. § 103 provides that a patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art." 35 U.S.C. § 103. Obviousness is a question of law that is predicated upon several factual inquiries. Richardson-Vicks v. Upjohn Co., 122 F.3d 1476, 1479 (Fed. Cir. 1997). Specifically, the trier of fact must consider four issues: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness, such as commercial success, long felt but unsolved need, failure of others, and acquiescence of others in the industry that the patent is valid, and

unexpected results. Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966)(the "Graham factors"). The Supreme Court, in KSR Intern. Co. v. Teleflex Inc., 127 S.Ct. 1727, 1734 (2007), reaffirmed that the Graham factors "continue to define the inquiry that controls" an obviousness analysis.

Because an issued patent is presumed valid, the party seeking to challenge the validity of a patent based on obviousness must demonstrate by clear and convincing evidence that the invention described in the patent would have been obvious to a person of ordinary skill in the art at the time the invention was made. Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1359-60 (Fed. Cir. 2007). Clear and convincing evidence is evidence that places in the fact finder "an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" Colorado v. New Mexico, 467 U.S. 310, 316 (1984).

A. The Prior Art

Whether the '406 Patent is prior art is a threshold inquiry in the statutory obviousness analysis. Obviousness is to be determined "at the time the invention was made," 35 U.S.C. § 103, and pertinent prior art includes only those references with effective dates prior to the date of invention, Kimberly-Clark Corp. v. Johnson & Johnson, 745 F.2d 1437, 1453 (Fed. Cir. 1984). "[T]he date of the invention is presumed to be the filing date of the parent application." Ecolochem, Inc. v. Southern California

Edison Co., 227 F.3d 1361, 1371 (Fed. Cir. 2000). This presumption can be rebutted, however, by a showing of either an earlier reduction to practice or an earlier conception and diligence in reduction to practice. See Price v. Symsek, 988 F.2d 1187, 1190 (Fed. Cir. 1993); Lifescan, Inc. v. Home Diagnostics, Inc., 103 F. Supp. 2d 345, 367 (D. Del. 2000).

The '406 patent application was filed on June 6, 1985, six months prior to the filing of the '122 patent application on December 6, 1985. The filing date of the '406 patent application is presumed to be its invention date, because no other evidence of an earlier date of invention was offered. Although the '406 patent application was filed before the '122 patent application, Proctor & Gamble contends that the '406 patent is not prior art because the '122 patent was actually conceived and reduced to practice before the invention date of the '406 patent. Because the filing date of the '122 application is its presumed invention date, Proctor & Gamble, as the party attempting to establish an earlier invention date, bears the burden of rebutting this presumption, by a preponderance of the evidence. Specifically, Proctor & Gamble must show that the '122 patent was conceived and diligently reduced to practice before June 6, 1985, the filing date of the '406 patent.[4] See Mahurkar v. C.R. Bard, Inc., 79

[4] To be clear, the ultimate burden of proving invalidity of the '122 patent remains with Teva. Pfizer, 480 F.3d at 1359.

F.3d 1572, 1576-77 (Fed. Cir. 1996)(borrowing burdens of proof from the interference context); see also 37 C.F.R. § 1.657(a).

Conception for purposes of chemical compounds requires the inventor to have a mental picture of the structure of the chemical compound, and possession of an operative method for making it. Oka v. Youssefyeh, 849 F.2d 581, 583 (Fed. Cir. 1998). When a party seeks to prove conception through oral testimony of a putative inventor, it must offer corroborating evidence. Chen v. Bouchard, 347 F.3d 1299, 1309 (Fed. Cir. 2003). In assessing corroborating evidence, courts apply a "rule of reason" analysis, in which "an evaluation of all pertinent evidence must be made so that a sound determination of the credibility of the inventor's story may be reached." Price, 988 F.2d at 1195. Lab notebooks, like any other documentary or physical evidence, are admissible without independent corroboration. Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1169 (Fed. Cir. 2006). Circumstantial evidence of an independent nature can satisfy the corroboration requirement. Cooper v. Goldfarb, 154 F.3d 1321, 1330 (Fed. Cir. 1998).

After reviewing the evidence relevant to conception, the Court concludes that Proctor & Gamble has not produced sufficient evidence to corroborate Dr. Benedict's oral testimony that he conceived of risedronate in May of 1985. (Benedict Tr. 420:19-421:22.) Proctor & Gamble attempted to corroborate this

testimony through physical evidence. Specifically, Proctor & Gamble submitted Dr. Benedict's signed and dated lab notebooks showing conception of risedronate on May 3, 1985, when recorded entries show that he synthesized the compound for the first time. (PTX 67.) The lab notebook also sets forth the chemical structure for risedronate and the chemical reactions utilized to synthesize risedronate. (Id.) However, Dr. Benedict's lab notebook was unwitnessed, and therefore, the Court accords it minimum corroborative value. Proctor & Gamble has offered no other independent corroborating evidence, and therefore, the Court concludes, as a matter of law, that Proctor & Gamble has failed to establish that the subject matter of the '122 patent was conceived prior to the filing date of the '406 patent. Because the Court concludes that an earlier conception date cannot be established, the Court need not consider the evidence as it relates to reduction to practice. Accordingly, the Court concludes that the '406 patent is properly considered prior art for purposes of determining whether the '122 patent is obvious.

B. The Level of Ordinary Skill in the Art

Having identified the relevant prior art, the Court must next determine the level of ordinary skill in the art at the time of the filing of the '122 patent. Relying on the testimony of Dr. Lenz, Teva contends that the relevant art for the '122 patent is the art of medicinal chemistry, and that a person skilled in

that art would have a Ph.D. in organic chemistry and several years experience in the field. (Lenz Tr. 77-78.) Further, such persons would have experience working with heterocyclic compounds, such as pyridine, and in interpreting biological activity and toxicity data. (Lenz Tr. 59, 73, 78-79.) Relying on the testimony of Dr. McKenna, Proctor & Gamble contends that, in the mid-1980s, a person of ordinary skill in the art relevant to the '122 patent would possess at least a Ph.D. in synthetic or bio-organic chemistry, as well as additional training in phosphorus chemistry. (McKenna Tr. 555.)

The Federal Circuit has identified several factors that may be used in determining the level of ordinary skill in the art, including but not limited to (1) the educational level of the inventor; (2) the types of problems encountered in the art; (3) the prior art solutions to those problems; (4) the rapidity with which innovations are made; (5) the sophistication of the technology; and (6) the educational level of active workers in the field. See, e.g., Envtl. Designs Ltd. v. Union Oil Co. of Calif., 713 F.2d 693, 696-697 (Fed. Cir. 1983). These factors need not be present in every case and certain factors may be more predominant in some cases than in others.

In the Court's view, Dr. McKenna's opinion concerning the level of one of ordinary skill in the art is more consistent with the factors identified by the Federal Circuit for making this

assessment. Accordingly, the Court concludes that training or experience in phosphorus chemistry is necessary for one to be considered a person of ordinary skill in the art relevant to the '122 patent in the mid-1980s. The Court notes that Teva's sole expert, Dr. Lenz, offered no opinions on whether the '122 patent would have been obvious to a person of ordinary skill in the art, where that person is defined as having additional training or experience in phosphorus chemistry. (Lenz Tr. 200.)

C. The Scope and Content of the Prior Art

For both its obviousness and double patenting contentions, the principle prior art reference that Teva relies on is the '406 patent, and in particular, claim 15 of the '406 patent. (Teva PFF 15.) The '406 Patent issued on August 2, 1988 to inventors Lawrence Flora and Benjamin Floyd, and is assigned to Proctor & Gamble.

The '406 patent discloses an "on-off" dosing regimen for administering bisphosphonates to a patient. (JTX 5; McKenna Tr. 608.) It addresses the central problem seen in bisphosphonates at the time, namely that they inhibited bone mineralization, by teaching the use of a cyclic administrative regimen to achieve a separation of the benign effect of anti-resorption from the unwanted side effect of anti-mineralization in patients. (McKenna Tr. 609.) The dosing regimen of the '406 patent includes a first period of administering the bisphosphonates over one to nine

days, followed by a rest period of about fifty to one-hundred twenty days. (JTX 5.) The patent lists thirty-six compounds with which the intermittent dosing regimen may be used, and identifies eight of those as preferred compounds. (Id.) The '406 Patent does not disclose risedronate. (McKenna Tr. 611.)

Claim 15 of the '406 Patent, when read alongside Claim 1, discloses a method of treating osteoporosis using a dosing regimen in which one of several bisphosphonates (including 2-pyr EHDP) is administered to the patient on a cyclical basis. Claim 15 recites:

> 15. A method for treating osteoporosis, in human or lower animals afflicted with or at risk to osteoporosis, comprising administering to said human or lower animal an effective amount of a bone resorption inhibiting polyphosphonate, wherein the bone resorption inhibiting polyphosphonates, and daily dosage ranges, are selected from the group consisting of:
>
> ethane-1-hydroxy-1,1-diphosphonic acid: from about 0.25 mg. P/kg to about 4 mg P/kg;
>
> Dichloromethane diphosphonic acid: from about 0.12 mg P/kg to about 5 mg P/kg;
>
> Propane-3-amino-1-hydroxy-1,1-diphosphonic acid: from about 0.025 mg P/kg to about 1 mg P/kg;
>
> Butane-4-amino-1-hydroxy-1,1-diphosphonic acid: from about 0.0025 mg P/kg to about 0.1 mg P/kg;
>
> Hexane-6-amino-1-hydroxy-1,1-diphosphonic acid: from about 0.025 mg P/kg to about 1 mg P/kg;
>
> 2-(2-pyridyl-ethane-1,1-diphosphonic acid:

> from about 0.0025 mg P/kg to about 0.1 mg P/kg;
>
> **[2-pyr EHDP]** 2-(2-pyridyl)-1-hydroxy-ethane-1,1-diphosphonic acid: from about 0.00025 mg P/kg to about 0.01 mg P/kg; and/or
>
> Hexahydroindan-2,2-diphosphonic acid: from about 0.25 mg P/kg to about 10 mg P/kg;
>
> and their pharmaceutically-acceptable salts and esters.

(JTX 5.)

Teva also identified eight drug products, none of which specifically targeted bone resorption or mineralization, existing prior to 1980 that contained pyridines and disclosed the conception, making, and/or testing of two or more pyridil positional isomers. (DTX 310; Lenz Tr. 98-105.)

D. Differences between the Claimed Subject Matter and Prior Art

Teva and Proctor & Gamble disagree in their accounts of what differences exist between the '406 Patent and '122 Patent, and whether such differences render the '122 patent obvious. The parties agree, however, that both patents are directed to the same problem, namely the impairment of bone mineralization caused by long-term use of bisphosphonates for the treatment of osteoporosis. (McKenna Tr. 634; Lenz Tr. 80-81.) With respect to the asserted claims of the '122 Patent, claim 4 recites risedronate as a chemical compound, claim 16 recites a pharmaceutical composition, and claim 23 defines a method of

treatment. (JTX 1; DTX 309, 311, 312.)

Risedronate and 2-pyr EHDP are both bisphosponates containing a "head" portion into which a hydroxy group is incorporated and a "tail" portion consisting of a "pyridine" ring, which is a six-membered ring consisting of five carbon atoms and one nitrogen atom. (DTX 307.) Being isomers, the only structural difference between the risedronate molecule and 2-pyr EHDP is the point of attachment of the pyridyl group to the linking carbon. (Id.) The linking carbon is attached to the pyridyl group at the 2 position in 2-pyr EHDP , and at the 3 position in risedronate, (id.), which is also known as 3-pyr EHDP, (Benedict Tr. 453.)

Teva contends that risedronate and 2-pyr EHDP have the same atomic composition and the same molecular weight, and that they differ only in the position of the nitrogen atom in the pyridine ring. (Lenz Tr. 92.) Proctor & Gamble contends that this difference is critical because, as a result of the difference in location of the nitrogen, 2-pyr EHDP and 3-pyr EHDP would have different physical, chemical, and biological properties. (McKenna Tr. 594-95.) Proctor & Gamble further contends that the resulting differences also include differences in charge distribution, polarity, and hydrogen bonding. (Id.) In this regard, Proctor & Gamble points out that Teva's expert, Dr. Lenz, admitted that he conducted no tests regarding these properties.

(Lenz Tr. 262, 264.)

In addition to the structural differences noted above, as well as the differences in charge distribution, polarity and hydrogen bonding, the Court also notes differences in the subject matter claimed by the '122 patent and the '406 patent. For example, the '122 patent discloses the design and making of new chemical compounds, (McKenna Tr. 609-10), whereas the '406 patent teaches the use of an intermittent regimen for dosing polyphosphonates. (Lenz Tr. 87-88; McKenna Tr. 608-09.) In addition, the '122 patent does not claim or make reference to the use of an intermittent dosing regimen, and the '406 patent does not claim any new chemical entities. (McKenna Tr. 609.)

Having examined the scope and content of the prior art and the differences between the prior art and the claimed invention in light of the ordinary skill in the art, the Court must determine whether those differences are sufficient to render the '406 patent an invalidating prior art reference. Teva contends that the '122 patent would have been obvious to one skilled in the art during the relevant time frame in light of the '406 patent because of (1) the structural similarity between risedronate and 2-pyr EHDP, (2) the '406 patent's disclosure of a method of treating osteoporosis using bisphosphonates, and (3) the standard technique in medicinal chemistry of making different pyridyl positional isomers. Further, Teva contends that Proctor

& Gamble can not rebut Teva's prima facie showing of obviousness because Proctor & Gamble has failed to demonstrate that risedronate shows "unexpected results."

In response, Proctor & Gamble contends that Teva has not established by clear and convincing evidence that the '122 patent would have been obvious in light of the '406 patent. Specifically, Proctor & Gamble contends that the '406 patent teaches away from the use of pyridil EHDP compounds given their inhibiting effects on bone mineralization, which the '406 patent's dosing regimen aimed to counteract. Further, Proctor & Gamble contends that a person of ordinary skill in the mid-1980s had no reasonable expectation that risedronate would be successful because there was, at that time, no reliable understanding of the structure-activity relationships of bisphosphonates. Lastly, Proctor & Gamble contends that the '122 patent would not have been obvious because of the unexpected results it showed with respect to potency and toxicity.

The Federal Circuit has held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007) (quoting In re Dillon, 919 F.2d 688, 692 (Fed. Cir.1990)). In

addition to structural similarities, the Federal Circuit has also required a showing of "'adequate support in the prior art'" for the change in structure. Id. (quoting In re Grabiak, 769 F.2d 729, 731-732 (Fed. Cir. 1985). Clarifying these principles further, the Federal Circuit has held that a prima facie case of unpatentability requires a "showing that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" Id.

The Federal Circuit has recently examined these principles in light of the Supreme Court's decision in KSR, and concluded that the test for prima facie obviousness for chemical compounds is "consistent with the legal principles enunciated in KSR." Although KSR rejected a rigid application of the teaching, suggestion or motivation test in an obviousness inquiry, the Federal Circuit noted that the Supreme Court still "acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in a way the claimed new invention does' in an obviousness determination." Id. at 1356-1357. In this regard, the Supreme Court further explained that there is no necessary inconsistency between the underlying idea of the teaching, suggestion, or motivation test and the Graham analysis so long as the teaching, suggestion or motivation test is not applied as a rigid and mandatory formula. Id. at 1357. In other words, the

Supreme Court has acknowledged that the teaching, suggestion, or motivation test "can provide 'helpful insight' to an obviousness inquiry." Id. (quoting KSR, 127 S.Ct. at 1731). Accordingly, "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." Id.

Reviewing the evidence adduced at trial in light of these legal principals, the Court concludes that Teva has not established by clear and convincing evidence that "the prior art would have suggested making the specific molecular modifications necessary" to achieve risedronate. Takeda, 492 F.3d at 1356. To begin, the Court is unpersuaded that a person of ordinary skill in the art would have selected 2-pyr EHDP as the "lead compound" out of the numerous compounds disclosed in the '406 patent. No specific claims in the '406 patent are directed specifically towards 2-pyr EHDP. Claims 17, 18, and 19 of the '406 patent specify the use of several non-pyridyl, non-nitrogen containing bisphosphonates in the claimed dosing regimen. (McKenna Tr. 612, 706-08.) Claim 15, which Teva focuses on, lists 2-pyr EHDP only as one of eight example compounds that could be used in the claimed intermittent dosing regimen. (JTX 5.)

Although prior art references other than the '406 patent had disclosed the conception or testing of pyridil positional

isomers, the Court is unpersuaded that, during the 1980s, such modifications would have been obvious in the field of bisphosphonates. Dr. Fleisch, the preeminent authority on bisphosphonates, wrote in 1984 that "every compound, while remaining a bisphosphonate, exhibits its own physical-chemical, biological and therapeutic characteristics, so that each bisphosphonate has to be considered on its own. To infer from one compound the effects in another is dangerous and can be misleading." (PTX 335 at 33; McKenna Tr. 572-573.) With respect to structure-activity relationships, Dr. Fleisch further observed that "[t]he potency of inhibiting bone resorption varies widely between different bisphosphonates and no relation has yet emerged between the structure of the bisphosphonate and its effect on bone resorption." (PTX 355 at 37; McKenna Tr. 573.)

In reaching these conclusions, the Court further notes that it is not persuaded by the testimony of Teva's expert, Dr. Lenz. Dr. Lenz's opinion was not consistent with the teachings of Dr. Fleish, a leading researcher in the areas of bone disease and bisphosphonate research in the mid-1980s. Further, the Court finds Dr. Lenz's opinions to be marred by hindsight. Indeed, Dr. Lenz admitted that he did not familiarize himself with bisphosphonates by reviewing drug profiles from the relevant time, but instead examined drug profiles in the current version of the Physician's Desk Reference. (Lenz Tr. 182-83, 193.)

In the alternative, however, the Court concludes that even if Teva can establish a prima facie case of obviousness, Proctor & Gamble has demonstrated sufficient evidence of unexpected results regarding risedronate's potency and toxicity to rebut such a prima facie showing. See In re Soni, 54 F.3d 746, 751 (Fed. Cir. 1995) (finding substantially improved and unexpected results sufficient to rebut a prima facie showing). Though Teva offers a differing interpretation of risedronate's potency and toxicity results, Proctor & Gamble has demonstrated to the Court's satisfaction that these testing results were unexpected and substantially improved over other bisphosphonates. Proctor & Gamble's testing of risedronate through both the TPTX and Schenk assays disclosed that it had an LED of 0.0003 mg P/kg/day.[5] (McOsker Tr. 726, 732.) At this level, the antiresorptive activity of risedronate was more than three times that of 2-pyr EHDP. (Benedict Tr. 476, 481-82.) Similarly, the toxicity profile of risedronate was three times superior to that of 2-pyr EHDP.[6] (Id., Miller Dr. 859-864.) Combined, risedronate

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[5]Results of the Schenk assay are expressed as a "lowest effective does" or "LED," which indicates the lowest dose at which a test compound inhibits bone resorption. (Miller Tr. 844.) The unit used are milligrams per kilogram per day (mg P/kg/day), which measures the amount of the drug administered relative to the weight of the animal being tested.

[6]Based on toxicity screenings, the NOEL (or "no observable effect level ") of risedronate was 0.75 mg P/kg/day, (Eastman Tr. 777-78), compared to a NOEL of 0.25 mg P/kg/day for 2-pyr EHDP. (Eastman Tr. 780-782.)

exhibited a safety to efficacy ratio that was at least ten times better than any of the other compounds tested. (Miller Tr. 867-68.) Especially in light of the inhibited bone mineralization caused by previous bisphosphonates, (Bilezikian Tr. 375-76), the Court credits testimony from Proctor & Gamble experts that risedronate's substantial superiority was unexpected. (Benedict Tr. 476, 479, 481; McOsker Tr. 726; Miller Tr. 870.) Accordingly, the Court concludes that even if Teva can demonstrate a prima facie case of obviousness, Proctor & Gamble has rebutted that showing by demonstrating risedronate's unexpected efficacy, and therefore, Teva cannot demonstrate that the '122 Patent was obvious in light of the prior art.

E. Secondary Considerations of Non-Obviousness

The Court's conclusion of non-obviousness is also supported by the secondary indicia of non-obviousness. In re Rouffet, 149 F.3d 1350, 1355 (Fed. Ct. 1998); Stratoflex, Inc. V. Aeroquip Corp., 713 F.2d 1530, 1539 (Fed. Cir. 1983). Among the secondary considerations that must be considered is the existence of a long-felt but unsolved need. Graham, 383 U.S. at 17-18. It is uncontested that, as of the mid-1980s, osteoporosis was recognized as a serious disease and that existing treatments were inadequate. (Bilezikian Tr. 366-68.) Coupled with the fact that risedronate, to a large extent, met this need, the longstanding, acute need for an effective osteoporosis drug supports the

determination that risedronate was nonobvious. Similarly, the Court's determination regarding risedronate's unexpected results, is also probative of risedronate's nonobviousness.

Proctor & Gamble also contends that the commercial success of risedronate strongly infers its nonobviousness. Teva does not dispute that risedronate, marketed under the brand name Actonel®, has been an "unequivocal commercial success." (Smith Tr. 961-62.) First available commercially in April 2000, Actonel® has achieved the status of a "blockbuster drug" and has generated sales of more than $2.7 billion. (Id.; DTX 124.) However, the Court accords little probative value to Actonel®'s commercial success, because risedronate's relevant prior art, the '406 patent, was assigned to Proctor & Gamble. Where the relevant community is blocked from acting on the prior art, the inference of non-obviousness from evidence of commercial success is weak. Merck & Co., Inc. v. Teva Pharma. USA, Inc., 395 F.3d 1364, 1377 (Fed. Cir. 2005). Here, the compound and the use of that compound against which the unobviousness of risedronate is measured was 2-pyr EHDP, which was known only to Proctor & Gamble. Accordingly, Actonel®'s undisputed commercial success is not particularly probative in finding nonobviousness. However, the other objective indicia relevant to nonobviousness support the Court's determination as discussed above.

F. Summary

In sum, the Court concludes that Teva has not demonstrated by clear and convincing evidence that the '122 patent is invalid as obvious. Taking into account the scope and content of the prior art and the differences between the asserted claims in the '122 patent and the '406 patent, the Court concludes that Teva has not established that the '122 patent would have been obvious to a person of ordinary skill in the art in the mid-1980s. Further, even if Teva had been able to make out a prima facie showing of obviousness, Proctor & Gamble has presented sufficient evidence of risedronate's unexpected properties to rebut such a showing. Accordingly, the Court cannot conclude that the '122 patent is invalid as obvious.

II. Whether the '122 Patent is Invalid for Obviousness-Type Double Patenting

In the alternative, Teva contends that the '122 patent is invalid for obviousness-type double patenting. Obviousness-type double patenting, also known as non-statutory double patenting, is a judicially created doctrine, the purpose of which is to preclude a patent owner from extending the right to exclude others from practicing his invention through claims in a later-filed patent that are not patentably distinct from claims in the earlier filed patent. Geneva Pharm., Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373, 1378 (Fed. Cir. 2003). The obviousness-type double patenting analysis involves two steps:

(1) the court must construe the claim in the earlier patent and the later patent and determine the differences between the two patents, and (2) the court must determine whether the differences in the subject matter between the two claims render the claims patentably distinct. Eli Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955, 968 (Fed. Cir. 2001)(citations omitted). The later claim is not patentably distinct from the earlier claim if it is anticipated by or obvious in light of the earlier claim. Id.

In general, the same type of analysis is used for an obviousness-type double patenting inquiry as for a Section 103 obviousness inquiry, with a focus on the first patent rather than prior art. See Affymetrix, Inc. v. PE Corp., 2002 WL 31875401 at *1 n.3 (S.D.N.Y. 2002); American Cyanamid Co. v. U.S. Surgical Corp., 833 F. Supp. 92, 127 (D. Conn. 1992). According to the Federal Circuit in Geneva Pharm., the distinctions between obviousness under section 103 and non-statutory double patenting include:

> 1. The objects of comparison are very different: Obviousness compares claimed subject matter to the prior art; nonstatutory double patenting compares claims in an earlier patent to claims in a later patent or application;
>
> 2. Obviousness requires inquiry into a motivation to modify the prior art; nonstatutory double patenting does not;
>
> 3. Obviousness requires inquiry into objective criteria suggesting non-obviousness; nonstatutory double patenting does not.

Geneva Pharm., 349 F.3d at 1378, n.1. Accordingly, the test for obviousness-type double patenting is narrower than the statutory obviousness inquiry. As in the statutory obviousness inquiry under 35 U.S.C. § 103, the '122 patent is presumably valid and Teva bears the burden of establishing invalidity by clear and convincing evidence. See Pfizer, 480 F.3d at 1360.

For all of the reasons discussed above in the broader statutory obviousness inquiry, the Court concludes that the asserted claims of the '122 patent are patentably distinct from claim 15 of the '406 patent. Unlike claim 15 of the '406 patent, which is directed to a specific "on-off" dosing regimen for administering bisphosphonates, claims 4, 16, and 23 of the '122 patent are unrelated to any particular dosing regimen and instead pertain to a novel compound and pharmaceutical composition comprising that compound. The '406 patent teaches away from modifying and using 2-pyr EHDP for treatment of bone disease without the claimed dosing regimen. After construing the relevant patents and determining the differences between them, see supra I. C. & D., the Court concludes that Teva has not established by clear and convincing evidence that the relevant claims of the '122 patent are patentably indistinct from claim 15 of the '406 patent, and therefore, the '122 patent is not invalid under the doctrine of obviousness-type double patenting.

CONCLUSION

For the reasons discussed, the Court concludes that Teva has not established that the '122 patent is invalid as obvious or for obviousness-type double patenting. Accordingly, the Court will enter judgment in favor of Proctor & Gamble and against Teva on Proctor & Gamble's claims of infringement. Proctor & Gamble shall submit, with notice to Teva, a proposed form of Final Judgment Order within ten days of the date of this Opinion and accompanying Order.[7]

[7] Proctor & Gamble has filed a Motion For Preliminary Injunction (D.I. 110) requesting the Court to enter a preliminary injunction until the Court has issued a final judgment and ordered a permanent injunction in this action. With entry of this decision, Proctor & Gamble's motion requesting preliminary injunctive relief is moot. To the extent Proctor & Gamble seeks entry of permanent injunctive relief, it should propose such language in its proposed form of judgment order.